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Original Article

THE EFFECTIVENESS OF TIGECYCLINE IN MULTIDRUG RESISTANT INFECTIONS IN INTENSIVE CARE UNIT

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ABSTRACT

Background

Infection with multidrug resistant (MDR) organism represent an important cause of a poor patient outcome, prolonged hospitalization and mortality. Patients in the intensive care unit at increased risk of developing these infections.

Aim

To evaluate the activity of tigecycline on MDR infection and to assess patient outcome.

Patients and Methods

Eleven patients, admitted to the intensive care unit at Ghazi Al-Hariri surgical hospital for the period from (Febuary 2016 to May 2016) whom infected with (MDR) organism documented by culture and sensitivity test results, received intravenous tigecycline and were assessed for outcome were included in the study.

Results

All the enrolled patients had infection resistance to the available antibiotics, the isolated (MDR) organisms were Klebsiella spp. (46%), Acinetobacter spp. (45%), and Enterobacteriace spp. (9%), causing sepsis in 60% and intra-abdominal infection in 40% of patients. Tigecycline was given at a median loading dose of (100mg), followed by a median maintenance dose of 50mg twice daily (100mg/day) for a median duration of (16 day. It was associated with better patient outcome (91%), discharged well from the hospital with median hospitalization periods of (1.4 month) and mortality of (9%).

Conclusion

Tigecycline was effective against (MDR) infection encountered in the ICU and was associated with better patient outcome.

KEYWORDS: Infection with Multidrug Resistant (MDR), Bacteria, Fungi, Viruses and Parasites

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INTRODUCTION

Antimicrobial resistance is the resistance of a microorganism to an antimicrobial drug that was originally

effective for treatment of infections caused by it. Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobial drugs, such as antibacterial drugs (e.g. Antibiotics), antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infections persist, increasing the risk of spread to others[1].

Antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi. It is, Antimicrobial resistance is present in all parts of the world,which represents a serious threat to global public health. The World health leaders have described antibiotic-resistant microorganisms as "nightmare bacteria", that "pose a catastrophic threat" to people in every country in the world for that, it requires action across all government sectors and society[2]. New resistance mechanisms emerge and spread globally[1].

Each year, at least 2 million people acquire serious infections with bacteria that are resistant to one or more of the antibiotics designed to treat those infections. In the United Statesleast 23,000 people die each year as a direct result of these antibiotic-resistant infections.Many more die from other conditions that were complicated by an antibiotic-resistant infection[1].

There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, bloodstream infections) in all regions of the world. A high percentage of hospital-acquired infections are caused by highly resistant bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA) or multidrug-resistant Gram-negative bacteria. Patients with infections caused by drug-resistant bacteria are generally at increased risk of worse clinical outcomes and death, and consume more healthcare resources than patients infected with the same bacteria that are not resistant[3].

Antimicrobial Resistance Jeopardy

The achievements of modern medicine are put at risk by antimicrobial resistance. Without effective antimicrobials for prevention and treatment of infections, the success of organ transplantation, cancer chemotherapy and major surgery would be compromised[4].

Present Situation from the WHO

WHO's 2014 report on global surveillance of antimicrobial resistance revealed that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill[5].

- Resistance to one of the most widely used antibacterial drugs for the oral treatment of urinary tract infections caused by *E. coli* – fluoroquinolones – is very widespread.
- Resistance to first-line drugs to treat infections caused by *staphylococcus aureus* – a common cause of severe infections acquired both in healthcare facilities and in the community – is also widespread[6].
    - Resistance to the treatment of last resort for life-threatening infections caused by common intestinal bacteria – carbapenem antibiotics – has spread to all regions of the world[5].

Tigecycline

Tigecycline, approved by the Food and Drug Administration (FDA) on June 15, 2005, is the first drug in this class of antimicrobials (glycylcycline). Alterations to the tetracycline structure allow tigecycline to maintain activity against tetracycline-resistant organisms, including resistant gram-positive organisms such as penicillin-resistant Strep to coccuspneumoniae, methicillin-resistant Staphylococcus aureus (MRSA) a Staphylococcus epidermidis (MRSE), and vancomycin-resistant Enterococcus (VRE) species. Tigecycline is approved for the treatment of complicated skin and skin structure infections (cSSSI) and complicated intraabdominalinfections caused by susceptible organisms[7]

Indications and Usage

FDA licensed indication[8]

- Complicated Skin and Skin Structure Infections
- Complicated Intra-abdominal Infections
- Community-Acquired Bacterial Pneumonia

Tigecycline received FDA approval in 2005 for the treatment of cSSSI and complicated intra-abdominal infections[7].

PATIENTS AND METHODS

Study Design

This was a hospital–based open label pilot study conducted at Ghazi Al-harry surgical hospital, Medical city, during the period from February 2016 to the end of May 2016, to determine the outcome of using tigecycline in patients infected with multi-drug resistant organisms (MDR)

Study Sample

Eleven patients infected with multi-drug resistant organisms (MDR), who was admitted to the intensive care unit (ICU) at Ghazi Al-harry surgical hospital whom received tigecycline vial (tygacil®50mg vial. Pfizer) were enrolled in this study.

Inclusion Criteria

Patients, who were infected with multi-drug resistant organisms (MDR), confirmed by culture and sensitivity test, adults, both genders, and who show no resolution of infection despite receiving the available antibiotic regimen, then they received an intravenous tigecycline treatment, were included in the study.

Exclusion Criterion

Patients with one or more of the following criteria were excluded from the study

- Pediatric age group
- Patients with *Pseudomonas erogenous* infections.
- Patients with hypersensitivity reactions or allergic to tetracyclines.

Data Collection

The data were collected by using a pre-structured form filled by the clinical pharmacist in the ICU ward by taking a clinical and laboratory data. Data regarding the clinical and demographic characteristics of the patients were reported, including: age, gender, infection, types, temperature, complete blood counts, culture and sensitivity test results, concomitant drugs, previous antibiotic used, duration of infection and the outcome.

Table 1: List of Materials Used

	Materials	Company
1.	Tygacil® 50mg vial	Pfizer, USA
2.	C/S test	High media, India

Duration of Treatment

Duration of treatment defined as the number of consecutive days in which, a patient had received tigecycline treatment till the outcome was reached.

The Outcome

The outcome was defined as resolution of infection when the patient no longer shows clinical signs of infection, deteriorated if patient transformed to another antibiotic other than tigecycline before the condition resolved, or dead for any cause of mortality in whom were still showing signs of infection after 14 days of tigecycline initiation.

Specimen Collection and Preparation for Analysis

- Sample where drown before the first dose of antibiotic is given
- Sample include sputum, urine, tip of the central venous line (CV line) was sent to the bacteriology lab. At at Ghazi Al-harry surgical hospital for analysis
- The results were received after 3-10 day.

Ethical Approval

- The study protocol was approved by the local protocols in the unit taken from the evidence based guidelines all over the world.
- The data and information of the patients were kept confidential and did not disclose to unauthorized personnel.

Statistical Analysis

Data of 11cases with suspected infection were analyzed by using the statistical package for social sciences (SPSS) software version 22, IBM, Chicago, US, for windows. Descriptive statistics were presented as median, frequencies (No.) and proportion (%). Finally, results were presented in tables and or figures with an explanatory paragraph.

RESULTS

Characteristics of the Enrolled Patients

A total of 11patients with different types of infections, who were receiving tigecycline therapy for documenting MDR infection have been enrolled in this study, their charecterists are shown in table (3-1).

Table 2: Characteristics of Studied Group (N=11)

	Median
Age	39
Gender (male/female)	7/4
Duration on previous antibiotics	8.5
Duration on tigecycline	16
Total hospitalization period	1.4
APACHE score	28

*APACHE scor =acute physiology and chronic health evaluation (severity of illness index)

Type of Infection

Types of infection are shown in figure (**Figure 3.1**).

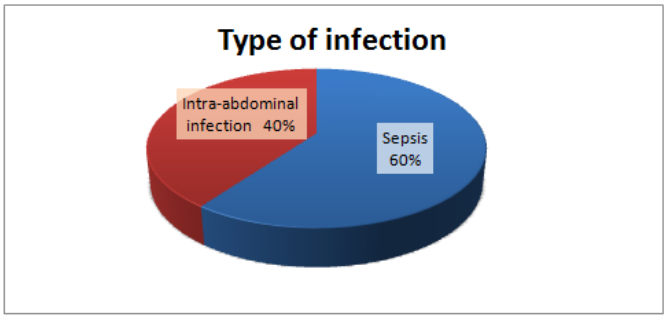

Figure 3.1: Type of Infection

While the figure (3.2) shows the encountered multidrug resistant bacteria as documented by the culture and sensitivity results obtained from different specimen type illustrated in table (3-2)

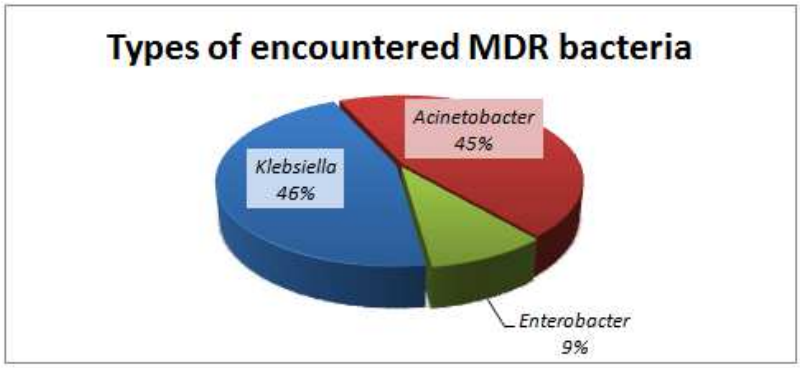

Figure 3.2: Types of Encountered MDR Bacterial Species

Tabel 3.2: Culture Speciemen Types.

Specimen	
Sputum	5
Blood	2
CVline*	1
Urine	2
Wound swab	1

*Central vien line tip

While the culture and sensitivity test antibiotic resistance patern are illustrated in figure (3.3)

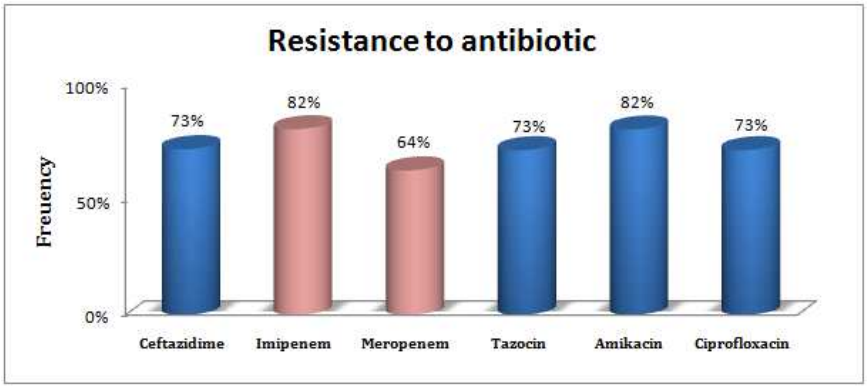

Figure 3.3: Antibiotic Resistance Frequency

Types of Previous Antibiotics Used

All enrolled patients received other antibiotics either in combination or a single agent prior to the initiation of tigecycline, (figure 3.3)

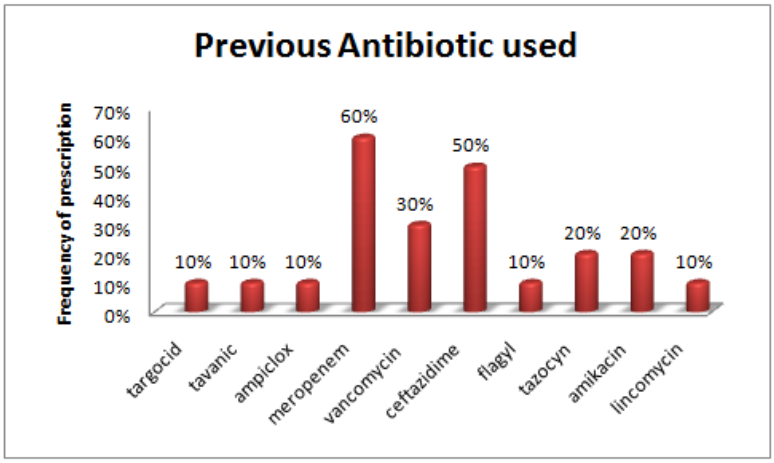

Figure 3.4: Types of Privious Antibiotic Used

The Outcome

Out of the11 patients, infection was resolved in 10,while 1 patient died (Figure 3.4).

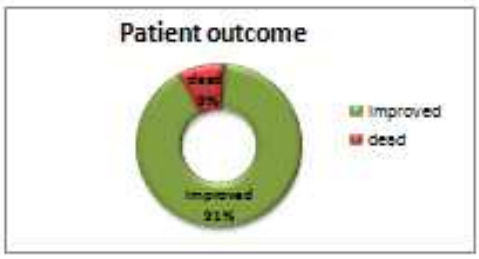

Figure 3.5: Patients Outcome

Charecteristica of Tigecycline Use

The use of tigecycline is sumerized in the following tabel:

Tabel 3: Tigecycline Use.

	Median	Range
Tigecycline loading dose (mg/dose)	100	100-200
Tigecycline maintenance dose (mg/day)	100	50-200
Number of vials used for each patient	30	4-86

DISCUSSIONS

Healthcare-associated infections (HAIs) are a leading cause of morbidity and mortality worldwide. Therapy is becoming ever more difficult, because of the increasing rate of antimicrobial resistance among common HAI pathogens[9]. According to the the European Antimicrobial Resistance SurveillanceSystem network (EARS-Net), over the lastdecade, multidrug-resistant Gram-negative bacteria(MDR-GNB), including MDR-*Pseudomonas aeruginosa*,MDR-*Acinetobacter baumannii* and*Enterobacteriaceae* producing extended-spectrum b-lactamases (ESBL) and carbapenemases, have been implicated in severe HAIs and theiroccurrence has increased steadily.[10]Infections caused by multidrug-resistant organisms are associated with prolonged medical care, worse outcome and costly therapies[9]. Specifically, at the intensive care unit (ICU),which often is called the epicenter of infections, the risk of mortality related to infection increase due to its extremely vulnerable population (reduced host defences deregulating the immune responses) and increased risk of becoming infected through multiple procedures and use of invasive devices distorting the anatomical integrity-protective barriers of patients (intubation, mechanical ventilation, vascular access, etc.) furthermore, mortality increased (up to fivefold) when the causal organisms were MDR[11].

Thus, applying strict infection control measures and proper choice of antibiotics that provide effective treatment are the corner stone for improving patient outcome.

As shown in this study MDR bacteria are an actual threat, where culture and sensativity test results revealed the infection with organism resistant to all the available antibiotics, leaving the patient at increased risk of death.

In this study, tigecycline showed improved patient outcome (as shown in figure 3.5 which illustrates 91% improvement in condition), which reflects the good activity against these MDR bacteria, hence it will be an effective weapon against these MDR bacteria, and thus providing another defencive line against morbidity and mortality caused by MDR.

CONCLUSIONS

- There is an actual risk of infection with multidrug resistant organism documented by culture and sensativity test result.
- The already available antibiotics failed to cure the infection in patient with MDR organism.
- Tigecycline was shown to be effective to improve the outcome in patient with MDR organisems.

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